Protocol Registration Receipt
06/12/2014

Grantor: CDER IND/IDE Number: 104,479 Serial Number:

28-day Repeat Dose Study of GSK573719

This study has been completed.

Sponsor:	GlaxoSmithKline
Collaborators:	GlaxoSmithKline
Information provided by (Responsible Party):	GlaxoSmithKline
ClinicalTrials.gov Identifier:	NCT01030965

Purpose

The study will evaluate the efficacy, safety, and pharmacokinetics of GSK573719 compared with placebo in subjects with COPD

Condition	Intervention	Phase
Pulmonary Disease, Chronic Obstructive	Drug: GSK573719 125mcg Drug: GSK573719 250mcg Drug: GSK573719 500mcg	Phase 2

Condition	Intervention	Phase
	Drug: Placebo	

Study Type: Interventional
Study Design: Treatment, Parallel Assignment, Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor), Randomized, Safety/Efficacy Study
Official Title: A Randomized, Double-blind, Parallel-group, Placebo-controlled Study to Evaluate the Efficacy and Safety of GSK573719 Delivered Once-daily Over 28 Days in Subjects With COPD

Further study details as provided by GlaxoSmithKline:

Primary Outcome Measure:

- Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 29 [Time Frame: Baseline and Day 29] [Designated as safety issue: No]

  FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 on Treatment Day 29 is defined as the mean of the FEV1 values obtained at 23 and 24 hours after dosing on Day 28. Baseline is defined as the mean of the FEV1 values obtained at 30 minutes and immediately pre-dose on Day 1. Change from Baseline is defined as the difference between trough on Day 29 and Baseline. Analysis was performed using a repeated measures model with covariates of Baseline (BL), country, sex, age, treatment, smoking status, day, day by Baseline interaction, and day by treatment interaction.

Secondary Outcome Measures:

- Change From Baseline in Weighted Mean 0-6 Hour FEV1 Obtained Post-dose at Day 1 and Day 28 [Time Frame: Baseline, Day 1, and Day 28] [Designated as safety issue: No]

  FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. The weighted mean FEV1 was derived by calculating the area under the FEV1/time curve (AUC), and then dividing the value by the time interval over which the AUC was calculated. The weighted mean was calculated using the 0-6 hour post-dose measurements at Days 1 and 28, which included pre-dose (30 minutes prior to dosing on Day 1, or 24 hours after the previous day's dose on Day 28), and post-dose at 15 minutes, 30 minutes, 1 hour, 3 hours, and 6 hours. Baseline is defined as the mean of the FEV1 values obtained at 30 minutes and immediately pre-dose on Day 1. Change from Baseline is defined as the difference between weighted mean at Days 1 and 28 and Baseline. Analysis was performed using a repeated measures model with covariates of Baseline, country, sex, age, treatment, smoking status, day, day by Baseline interaction, and day by treatment interaction.
- Change From Baseline in Serial FEV1 Over 24 Hours After Dosing at Day 1 and Day 28 [Time Frame: Baseline, Day 1, and Day 28] [Designated as safety issue: No]

  Serial spirometry assessments were conducted on Day 1 and Day 28 over the course of 24 hours and were obtained 0 (Day 28 only), 1, 3, 6, 23, and 24 hours after dosing. Baseline is defined as the mean of the FEV1 values obtained at 30 minutes and immediately pre-dose on Day 1. Change from Baseline is defined as the difference between FEV1 on Days 1 and 28 and Baseline.

Enrollment: 287
Study Start Date: December 2009
Study Completion Date: July 2010
Primary Completion Date: July 2010

Arms	Assigned Interventions
Experimental: GSK573719 125mcg 125mcg once-daily via novel dry powder inhaler	Drug: GSK573719 125mcg 125mcg once-daily
Experimental: GSK573719 250mcg 250mcg once-daily via novel dry powder inhaler	Drug: GSK573719 250mcg 250mcg once-daily
Experimental: GSK573719 500mcg 500mcg once-daily via novel dry powder inhaler	Drug: GSK573719 500mcg 500mcg once-daily
Placebo Comparator: Placebo once-daily via novel dry powder inhaler	Drug: Placebo once-daily

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate 3 doses of GSK573719 administered once-daily over 28 days in subjects with COPD.

Eligibility

Ages Eligible for Study: 40 Years to 80 Years
Genders Eligible for Study: Both

Inclusion Criteria:

- A signed and dated written informed consent prior to study participation
- Males or females of non-childbearing potential

- 40 to 80 years of age
- COPD diagnosis
- 10 pack-years history or greater of cigarette smoking
- Post-bronchodilator FEV1/FVC ratio of 0.70 or less
- Post-bronchodilator FEV1 of 25 to 70% of predicted normal

Exclusion Criteria:

- Asthma
- Other significant respiratory disorders besides COPD, including alpha-1 deficiency
- Previous lung resection surgery
- Chest X-ray or CP scan showing clinically significant abnormalities not due to COPD
- Use of oral steroids or antibiotics for a COPD exacerbation within 6 weeks of screening
- Hospitalization for COPD or pneumonia within 3 months of screening
- Any significant disease that would put subject at risk through study participation
- BMI greater than 35
- Pacemaker
- Significantly abnormal ECG or clinical lab finding (including Hepatitis B or C)
- Cancer
- Allergy or hypersensitivity to anticholinergics or inhaler excipients
- Diseases that would contraindicate the use of anticholinergics
- Use of oral corticosteroids within 6 weeks of screening
- Use of long-acting beta-agonists within 48 hours of screening
- Use of tiotropium within 14 days of screening
- Use of theophyllines or anti-leukotrienes within 48 hours of screening
- Use of short-acting bronchodilators within 4 to 6 hours of screening
- Use of investigational medicines within 30 days of screening
- Use of high dose inhaled corticosteroids
- Use of long-term oxygen therapy, CPAP or NIPPV
- Participation in acute phase of pulmonary rehabilitation program
- History of alcohol or drug abuse within 2 years prior to screening
- History of psychiatric disease limiting validity of consent
- Affiliation with the investigative site
- Previous use of GSK573719

Contacts and Locations

Locations

United States, Kentucky

GSK Investigational Site

Madisonville, Kentucky, United States, 42431

United States, North Carolina

GSK Investigational Site

Charlotte, North Carolina, United States, 28207

United States, South Carolina

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Tallinn, Estonia, 13419

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Berlin, Berlin, Germany, 14057

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Investigators

Study Director:	GSK Clinical Trials	GlaxoSmithKline

More Information

Publications:

Decramer M, Maltais F, Feldman G, Brooks J, Harris S, Mehta R, Crater G. Bronchodilation of umeclidinium, a new long-acting muscarinic antagonist, in COPD patients. Respir Physiol Neurobiol. 2013;185(2):393-399.

Responsible Party:	GlaxoSmithKline
Study ID Numbers:	113589
Health Authority:	Estonia: State Agency of Medicines Germany: Bundesinstitut für Arzneimittel und Medizinprodukte Poland: Ministry of Health & Social Welfare United States: Food and Drug Administration

Study Results

Participant Flow

Pre-Assignment Details

The study consisted of a Run-in Period of 5 to 8 days, followed by a 28-day Treatment Period. A total of 421 participants were screened; of these, 125 were screen failures, 10 were Run-in failures, 288 were randomized, and 285 received at least one dose of study drug (three participants were randomized but did not receive study drug).

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 28 days.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 28 days.
UMEC 250 µg	Participants received UMEC 250 µg QD in the morning via a DPI for 28 days.
UMEC 500 µg	Participants received UMEC 500 µg QD in the morning via a DPI for 28 days.

Overall Study

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
Started	71	71	72	71
Completed	67	65	68	64

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
Not Completed	4	6	4	7
Lack of Efficacy	3	2	0	3
Protocol Violation	1	1	1	1
Adverse Event	0	1	2	1
Protocol-defined Stopping Criteria	0	1	1	0
Withdrawal by Subject	0	1	0	2

Baseline Characteristics

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 28 days.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 28 days.
UMEC 250 µg	Participants received UMEC 250 µg QD in the morning via a DPI for 28 days.
UMEC 500 µg	Participants received UMEC 500 µg QD in the morning via a DPI for 28 days.

Baseline Measures

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg	Total
Number of Participants	71	71	72	71	285

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg	Total
Age, Continuous [units: Years] Mean (Standard Deviation)	62.3 (6.80)	60.1 (8.75)	60.3 (8.45)	62.6 (9.30)	61.4 (8.41)
Gender, Male/Female [units: Participants]					
Female	24	35	30	34	123
Male	47	36	42	37	162
Race/Ethnicity, Customized [units: Participants]					
African American/African Heritage	1	4	3	1	9
White	70	67	69	69	275
African American/African Heritage & White	0	0	0	1	1

Outcome Measures

1. Primary Outcome Measure:

Measure Title	Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 29
Measure Description	FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. Trough FEV1 on Treatment Day 29 is defined as the mean of the FEV1 values obtained at 23 and 24 hours after dosing on Day 28. Baseline is defined as the mean of the FEV1 values obtained at 30 minutes and immediately pre-dose on Day 1. Change from Baseline is defined as the difference between trough on Day 29 and Baseline. Analysis was

	performed using a repeated measures model with covariates of Baseline (BL), country, sex, age, treatment, smoking status, day, day by Baseline interaction, and day by treatment interaction.
Time Frame	Baseline and Day 29
Safety Issue?	No

Analysis Population Description

Intent-to-Treat (ITT) Population: all participants randomized to treatment who received >=1 dose of randomized study medication in the treatment period. All participants with >=1 post-BL assessment and non-missing covariate data are included in the analysis. The number of participants represents participants who provided data at Day 29.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 28 days.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 28 days.
UMEC 250 µg	Participants received UMEC 250 µg QD in the morning via a DPI for 28 days.
UMEC 500 µg	Participants received UMEC 500 µg QD in the morning via a DPI for 28 days.

Measured Values

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
Number of Participants Analyzed	67	64	68	64
Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1)	0.013 (0.025)	0.171 (0.025)	0.181 (0.025)	0.163 (0.025)

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
at Day 29 [units: Liters] Least Squares Mean (Standard Error)				

Statistical Analysis 1 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 29

Groups	Placebo, UMEC 125 µg
Method	Other [Repeated Measures Analysis of Covariance]
P-Value	<0.001
Mean Difference (Final Values)	0.159
95% Confidence Interval	0.088 to 0.229

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Statistical Analysis 2 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 29

Groups	Placebo, UMEC 250 µg
Method	Other [Repeated Measures Analysis of Covariance]
P-Value	<0.001
Median Difference (Final Values)	0.168
95% Confidence Interval	0.099 to 0.238

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

Statistical Analysis 3 for Change From Baseline in Trough Forced Expiratory Volume in One Second (FEV1) at Day 29

Groups	Placebo, UMEC 500 µg
Method	Other [Repeated Measures Analysis of Covariance]
P-Value	<0.001
Mean Difference (Final Values)	0.150
95% Confidence Interval	0.080 to 0.220

Additional details about the analysis, such as null hypothesis and power calculation:

[Not specified.]

Additional information, such as whether or not the p-value is adjusted for multiple comparisons and the a priori threshold for statistical significance:

[Not specified.]

Other relevant information, such as adjustments or degrees of freedom:

[Not specified.]

2. Secondary Outcome Measure:

Measure Title	Change From Baseline in Weighted Mean 0-6 Hour FEV1 Obtained Post-dose at Day 1 and Day 28
Measure Description	FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. The weighted mean FEV1 was derived by calculating the area under the FEV1/time curve (AUC), and then dividing the value by the time

	interval over which the AUC was calculated. The weighted mean was calculated using the 0-6 hour post-dose measurements at Days 1 and 28, which included pre-dose (30 minutes prior to dosing on Day 1, or 24 hours after the previous day's dose on Day 28), and post-dose at 15 minutes, 30 minutes, 1 hour, 3 hours, and 6 hours. Baseline is defined as the mean of the FEV1 values obtained at 30 minutes and immediately pre-dose on Day 1. Change from Baseline is defined as the difference between weighted mean at Days 1 and 28 and Baseline. Analysis was performed using a repeated measures model with covariates of Baseline, country, sex, age, treatment, smoking status, day, day by Baseline interaction, and day by treatment interaction.
Time Frame	Baseline, Day 1, and Day 28
Safety Issue?	No

Analysis Population Description

ITT Population. Participants (par.) with >=1 post-BL assessment and non-missing covariate data are included in the analysis. Different par. may have been analyzed at different time points (n=X, X, X, X in the category titles), so the overall number of par. analyzed reflects everyone in the ITT Population with data avaialable at >=1 time point.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 28 days.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 28 days.
UMEC 250 µg	Participants received UMEC 250 µg QD in the morning via a DPI for 28 days.
UMEC 500 µg	Participants received UMEC 500 µg QD in the morning via a DPI for 28 days.

Measured Values

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
Number of Participants Analyzed	70	71	72	70
Change From Baseline in Weighted Mean 0-6 Hour FEV1 Obtained Post-dose at Day 1 and Day 28 [units: Liters] Least Squares Mean (Standard Error)				
Day 1, n=70, 70, 71, 70	0.005 (0.015)	0.211 (0.015)	0.224 (0.014)	0.173 (0.015)
Day 28, n=65, 64, 68, 64	0.009 (0.024)	0.220 (0.024)	0.204 (0.023)	0.122 (0.024)

3. Secondary Outcome Measure:

Measure Title	Change From Baseline in Serial FEV1 Over 24 Hours After Dosing at Day 1 and Day 28
Measure Description	Serial spirometry assessments were conducted on Day 1 and Day 28 over the course of 24 hours and were obtained 0 (Day 28 only), 1, 3, 6, 23, and 24 hours after dosing. Baseline is defined as the mean of the FEV1 values obtained at 30 minutes and immediately pre-dose on Day 1. Change from Baseline is defined as the difference between FEV1 on Days 1 and 28 and Baseline.
Time Frame	Baseline, Day 1, and Day 28
Safety Issue?	No

Analysis Population Description

ITT Population. All participants with >=1 post-BL assessment and non-missing covariate data are included in the analysis. Different participants may have been analyzed at different time points (represented by n=X, X, X, X in the category titles), so the overall number of participants analyzed reflects everyone in the ITT Population.

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 28 days.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 28 days.
UMEC 250 µg	Participants received UMEC 250 µg QD in the morning via a DPI for 28 days.
UMEC 500 µg	Participants received UMEC 500 µg QD in the morning via a DPI for 28 days.

Measured Values

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
Number of Participants Analyzed	71	71	72	71
Change From Baseline in Serial FEV1 Over 24 Hours After Dosing at Day 1 and Day 28 [units: Liters] Least Squares Mean (Standard Error)				
Day 1, 1 hour, n=70, 71, 72, 71	0.013 (0.015)	0.196 (0.015)	0.212 (0.015)	0.145 (0.015)
Day 1, 3 hours, n=70, 71, 72, 71	0.008 (0.018)	0.255 (0.018)	0.274 (0.018)	0.227 (0.018)
Day 1, 6 hours, n=70, 71, 72, 70	-0.004 (0.019)	0.232 (0.019)	0.221 (0.019)	0.186 (0.019)
Day 1, 23 hours, n=70, 70, 72, 70	-0.036 (0.019)	0.171 (0.019)	0.186 (0.019)	0.107 (0.019)
Day 1, 24 hours, n=69, 71, 72, 70	-0.002 (0.019)	0.211 (0.018)	0.216 (0.018)	0.153 (0.018)
Day 28, 0 hours, n=67, 64, 69, 65	-0.017 (0.024)	0.165 (0.024)	0.203 (0.024)	0.140 (0.024)

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
Day 28, 1 hour, n=67, 64, 68, 65	-0.008 (0.025)	0.207 (0.026)	0.182 (0.025)	0.067 (0.026)
Day 28, 3 hours, n=67, 65, 67, 64	0.008 (0.026)	0.267 (0.026)	0.204 (0.026)	0.168 (0.026)
Day 28, 6 hours, n=65, 65, 68, 64	-0.005 (0.028)	0.206 (0.028)	0.181 (0.027)	0.141 (0.028)
Day 28, 23 hours, n=67, 64, 68, 64	-0.013 (0.026)	0.144 (0.027)	0.161 (0.026)	0.157 (0.027)
Day 28, 24 hours, n=67, 64, 68, 64	0.024 (0.025)	0.204 (0.026)	0.192 (0.025)	0.170 (0.026)

Reported Adverse Events

Reporting Groups

	Description
Placebo	Participants received matching placebo once daily (QD) in the morning via a dry powder inhaler (DPI) for 28 days.
UMEC 125 µg	Participants received umeclidinium bromide (UMEC) 125 micrograms (µg) QD in the morning via a DPI for 28 days.
UMEC 250 µg	Participants received UMEC 250 µg QD in the morning via a DPI for 28 days.
UMEC 500 µg	Participants received UMEC 500 µg QD in the morning via a DPI for 28 days.

Time Frame

On-treatment serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of study medication up to 4 weeks.

Additional Description

On-treatment serious adverse events (SAEs) and non-serious AEs are reported for members of the Intent-to-Treat (ITT) Population, comprised of all participants randomized to treatment who received at least one dose of randomized study medication in the treatment period.

Serious Adverse Events

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
Total # participants affected/at risk	0/71 (0%)	1/71 (1.41%)	1/72 (1.39%)	1/71 (1.41%)
Eye disorders				
Retinal detachment † [A]				
# participants affected/at risk	0/71 (0%)	1/71 (1.41%)	0/72 (0%)	0/71 (0%)
# events				
Infections and infestations				
Gastroenteritis viral † [A]				
# participants affected/at risk	0/71 (0%)	0/71 (0%)	0/72 (0%)	1/71 (1.41%)
# events				
Respiratory, thoracic and mediastinal disorders				
Chronic obstructive pulmonary disease † [A]				
# participants affected/at risk	0/71 (0%)	0/71 (0%)	1/72 (1.39%)	0/71 (0%)
# events				

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

Other Adverse Events

Frequency Threshold Above Which Other Adverse Events are Reported: 3%

	Placebo	UMEC 125 µg	UMEC 250 µg	UMEC 500 µg
Total # participants affected/at risk	6/71 (8.45%)	5/71 (7.04%)	9/72 (12.5%)	13/71 (18.31%)
Infections and infestations				
Nasopharyngitis † [A]				
# participants affected/at risk	3/71 (4.23%)	2/71 (2.82%)	1/72 (1.39%)	2/71 (2.82%)
# events				
Nervous system disorders				
Headache † [A]				
# participants affected/at risk	3/71 (4.23%)	3/71 (4.23%)	4/72 (5.56%)	6/71 (8.45%)
# events				
Respiratory, thoracic and mediastinal disorders				
Cough † [A]				
# participants affected/at risk	2/71 (2.82%)	0/71 (0%)	6/72 (8.33%)	8/71 (11.27%)
# events				

† Indicates events were collected by systematic assessment.

A Term from vocabulary, MedDRA

More Information

Certain Agreements:

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

GSK agreements may vary with individual investigators, but will not prohibit any investigator from publishing. GSK supports the publication of results from all centers of a multi-center trial but requests that reports based on single-site data not precede the primary publication of the entire clinical trial.

Limitations and Caveats:

Results Point of Contact:

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